CASE REPORT

Cardiac Effects of Lithium Therapy: Tailoring Treatment Decisions

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Abstract

Lithium is invaluable in the management of bipolar disorders and treatment-resistant depression. However, its narrow therapeutic-toxicity index warrants regular monitoring of its serum level. It is also associated with cardiac complications at both therapeutic and toxic levels and even with abnormalities present on electrocardiogram (ECG), patients can present asymptomatically, emphasising the need for regular ECG. Females from the older age group are additionally more prone to developing hypothyroidism which can cause sinus node dysfunction, hence thyroid function too needs to be monitored. Polypharmacy and drug-drug interactions may also increase the level of serum lithium, leading to side-effects and lithium toxicity. We present two cases of cardiac complications of lithium therapy whereby treatment options differed and fortunately worked to the benefit of both patients.

Keywords: Lithium Toxicity, Cardiac Arrhythmias, Junctional Bradycardia, Nodal Bradycardia, Sinus Node Dysfunction

Introduction

Lithium salt, a mood stabiliser, has been well known for its use in the field of psychiatry mainly in the management of bipolar disorders and treatment-resistant depression. It is available in Malaysia as a lithium carbonate preparation and is almost wholly excreted by the kidneys. Due to its unfortunate narrow therapeutic-toxicity index, it can affect the heart and endocrinal system, as well as causing nephrogenic, neurological and gastrointestinal abnormalities in some individuals [1]. Therefore, monitoring is necessary and vital in those on lithium therapy.

Lithium is associated with a wide range of cardiac complications at both therapeutic and toxic levels (Table 1) and that will be

the main focus of our report. Even with abnormalities present on electrocardiogram (ECG), patients may present without symptoms and this emphasises the need for regular ECG monitoring in those on lithium therapy. Females, especially from the older age group, who are prescribed lithium are additionally more prone to developing hypothyroidism as compared to males with the same treatment, necessitating a mention of thyroid-related complications of treatment with lithium as it has been found that features of hypothyroidism usually precede ECG changes [2] and have been known to decrease cardiac output, as well as a propensity to cause hypercalcaemia which can also have cardiovascular effects.

The possibility of polypharmacy should also be considered, as symptoms of increase in temperature, blood pressure and pulse rate may occur when taking combinations of lithium and neuroleptic medications [1]. Drug-drug interactions may also increase the level of serum lithium by promoting reabsorption and reducing its excretion, producing side-effects and lithium toxicity [1].

We hereby present two cases of cardiac complications of lithium therapy whereby treatment could be continued thereafter at a lowered dose in one patient but had to be terminated in the other as a result of its cardiac effects. Consent was obtained from both patients prior to preparing this manuscript and the Patient Review and Research committee of Penang Adventist Hospital was then informed of this endeavor and approval was granted.

Case Reports

Patient A

A 70-year old Indian lady with no known medical illness and only family history of type II diabetes mellitus and ischaemic heart disease was diagnosed with bipolar II disorder 20 years ago. She presented eight years ago for continuation of care and was on escitalopram, lamotrigine and quetiapine prescribed by her doctor in India.

Her symptoms were well-managed even after the antidepressant was stopped for another two years until she began experiencing depressive symptoms consisting of low confidence and early morning awakening. Lithium was then added to the regime to augment her existing mood stabiliser. She initially tolerated it well at a dose of 300mg daily and serum levels were maintained within the therapeutic range during the course of treatment. Given the possibility of QT prolongation when lithium and quetiapine are given together, it was not planned for her dose of lithium to be further increased. Her diabetic medication consisting of levemir, dapagliflozin and a metformin-sitagliptin combination were not as much a concern as compared to her cardiac ones such as losartan, lercanidipine hydrochloride, carvedilol and clopidogrel, all known to have interactions with lithium.

A couple of years after that, she insidiously began to feel generally unwell but with vague symptoms. Junctional (or nodal) bradycardia was discovered on routine investigative ECG and she was advised by her cardiologist to withhold the lithium. Her thyroid function was within the normal range with free T4 level of 9.9 ng/mL and TSH level of 1.429 uIU/mL. Her calcium level done at another hospital was confirmed to be within the normal range. The dose of lamotrigine was increased from 50 mg to 200 mg daily while she continued to be on 300 mg of quetiapine nocte. The bradycardia improved upon discontinuation of lithium

but she reported experiencing essential tremors for three weeks despite discontinuing the said medication, upon which exploration found to be anxiety-related.

She then presented with depressive symptoms and complained of sleep problems since cessation of lithium therapy. A decision was then made to restart lithium at a dosage of 150 mg daily and this low dose justified its continued use as opposed to the risk of destabilising her bipolar status. Thereafter, there have been no reported incidences of bradycardia that could have been caused by any of her existing cocktail of cardiac medications, nor of tremors, and she has been in remission since.

Table 1. Cardiac complications of lithium

Therapeutic Level	Toxic Level
• Non-specific T-wave changes – flattenings or inversions • Sinus node dysfunction (i.e. sinus bradycardia)	• Sinoatrial block • Atrial fibrillation/flutter • Intraventricular conduction delay • ST depressions/elevations • Unmasking of Brugada pattern • Atrioventricular conduction delay • QT_c prolongation • QTdR changes • Ventricular tachycardia/fibrillation • Myocarditis/cardiomyopathy

Patient B

An 82-year old Chinese lady with a background history of gout, hypertension and hyperlipidaemia was diagnosed with major depressive disorder (MDD) in Singapore 16 years ago and had been on mirtazapine after responding well to two courses of electroconvulsive therapy (ECT). She was started on lithium five years ago when she had breakthrough depressive symptoms but it was taken off two years later after she suffered a stroke resulting in right hemiparesis.

She presented in a relapsed state of depressive stupor soon after transfer of her care and began improving after receiving her third session of ECT. She was re-admitted a day after her weekend discharge for post-ECT delirium and was subsequently restarted on lithium during that admission

after the confusional state cleared considering the positive response she had when on it previously. Throughout the course of her treatment with lithium at a dose of 450mg nocte, serum levels remained within the therapeutic range and there were no reported issues with regards to her regime, which included an increased mirtazapine dose to 60mg nocte.

She then suddenly began experiencing shortness of breath, had right flank pain and was found to be bradycardic last year and a diagnosis of acute coronary syndrome was made by her cardiologist. Her thyroid function test revealed normal values for free T3 (13.4 ng/mL), free T4 (5.79 ng/mL) and TSH levels (1.6 uIU/mL). Her calcium level done at a different hospital was also reported to be normal. She was incidentally found to have mild renal impairment with a raised urea level of 13.1 mmol/L and creatinine level of 136 umol/L. As a precaution, lithium was withheld as it may have affected adequate renal clearance. Her physical symptoms progressively improved and she was then started on lamotrigine a month later for prophylaxis. However, her psychological condition began to deteriorate and a decision to combine her regime with a minimal dose of lithium at 75 mg daily was made, to which she responded and continued to improve over the following two months.

Whilst still tapering off lithium after going into remission, she presented to the emergency department with loss of consciousness associated with a fall, whereby she had no recollection of the event. Her ECG showed junctional bradycardia with pauses and lithium was then immediately stopped. A review of her other medications found no recent new drug introductions, nor were the dosages of her existing drugs up-titrated. Although she was not on any thiazide diuretics, some of the other medications she was on, namely trimetazidine, clopidogrel and amlodipine, have been known culprits in increasing lithium levels and thus re-inforced the decision to keep her off lithium.

Her physical condition gradually improved and the dose of lamotrigine was increased to 150mg daily and she has fortunately managed to remain in remission since, even after recent reductions in the dosage of mirtazapine to 45mg nocte. No further episodes of bradycardia recurred thereafter, thus excluding the beta-blocker she was on as the other possible causative candidate for her bradycardia. Omitting lithium also avoided a pacemaker insertion had it been deemed imperative for it to be continued.

Discussion

Non-specific T-wave changes and sinus node dysfunction are commonly seen even within therapeutic levels of treatment with lithium. However, when levels are within the toxic range, the associated problems are sinoatrial block, intraventricular conduction delay, ST depressions or elevations, unmasking of Brugada pattern, atrioventricular conduction delays, QT prolongation and other potentially life threatening effects [2]. The cardiac effects of lithium toxicity could potentially lead to ventricular instability, cardiac arrhythmias and even sudden cardiac arrest [2]. Transient myocarditis, dilated cardiomyopathy (including Takotsubo “stress” cardiomyopathy) have also been associated with lithium intoxication [3,4]. Additionally, concomitant use of ACE inhibitors, angiotensin receptor blockers (ARBs) or thiazide diuretics may increase lithium levels.

Lithium blocks the sodium channels found in the sinoatrial node and the tissue surrounding it, resulting in bradycardia [5]. These voltage-gated sodium channels are involved in the depolarisation of the cardiac cells. As a result of this blockage, the rate of sinoatrial node depolarisation decreases and hence leads to sinus bradycardia. This appeared to be the probable problem experienced by both of our patients. Blockage of the sodium channels also causes a reduction in intracellular potassium and hyperkalemia then ensues by the replacement of potassium, thereby causing arrhythmias. Furthermore, bradycardia seen in those on lithium therapy could be due to the potential of lithium interfering with the channels responsible for sinus node pacemaker activity. Nevertheless, lithium-induced sinus node dysfunction does not occur in all patients on lithium – this suggests that there are other factors that may contribute to this such as unstable serum lithium levels, intrinsic parasympathetic and sympathetic tone, age-related interstitial fibrosis causing decrease in sinus rate, various cardiac sodium channel expressions and underlying cardiac disease [6]. These dysfunctions are also more commonly seen in those on long-term lithium treatment than those on short-term treatment.

Although ECG changes are usually reversible once lithium is withheld, it still has the potential to turn into irreversible sinus node dysfunction with recurrent bradycardia and a patient may end up with a temporary or permanent pacemaker, the latter being an option for those who continue requiring lithium therapy to manage their symptoms [7]. Sadly, the reversible nature of this conduction abnormality cannot be guaranteed should a patient resume lithium therapy as irreversibility may be triggered by a decreased number of cells in the sinus node as one ages. Finally, long-standing asymptomatic sinus node dysfunction has to be kept in mind and therefore, closer follow-ups would then be prudent if lithium therapy is to be continued [8]. In patients with symptomatic or clinically significant true drug-induced bradycardia, the decision as to whether to stop, reduce the incriminating drug or to continue it after inserting pacing therapy if there is no acceptable alternative [9] has to be made, of which the first two options were chosen for our respective patients.

Where the frequency of cardiac monitoring for patients on lithium therapy is concerned, there are no mandatory guidelines for it and studies show that frequent ECG monitoring of either those subjects on lithium within the therapeutic level and those with high serum lithium concentration provides no further benefit as it may only show minor changes and is therefore unnecessary. Patients with metabolic syndrome and a strong family history of ischaemic heart disease or kidney problems are more prone to lithium toxicity and both of our patients, in addition to being in the older age group, have either a family history or risk factors for cardiac disease and metabolic syndrome, hence a baseline ECG and cardiac monitoring every six to 12-monthly would be recommended [2]. The nature of mood disorders, which frequently affect the level of physical activity and appetite, subsequently put patients at particular risk of developing truncal obesity [10]. This type of obesity is associated with increased risks of developing hypertension, dyslipidaemia, ischaemic heart disease, stroke, as well as increased mortality. Furthermore, antipsychotics, which are often taken by the patients in combination with lithium for bipolar disorder, have been known to affect the lipid levels of patients. These predisposing factors, in addition to the cardiac side effects and possible toxicity

of lithium, may exacerbate any underlying cardiac conditions [10].

Hypothyroidism can also lead to sinus node dysfunction [11], resulting in a lowered heart rate. ECG changes are determined by age, duration of therapy, and serum lithium and potassium levels [2,12]. 85.7% of people above the age of 40 have been found to have ECG changes and amongst those taking lithium treatment for a period of greater than two years, 90.9% of them were observed to have changes in their ECG [12]. Fortunately, neither of our patients developed hypothyroidism from lithium therapy but it is nonetheless something to be watched out for.

Management

A basic protocol for monitoring patients using lithium is therefore vital. It is very important that the list of concurrent medications be updated at each clinic visit. It is also essential to keep a patient on lithium adequately hydrated to prevent an increase in its serum level. Patients on high doses of treatment should be periodically assessed for lithium toxicity. Other than watching out for clinical signs, the Amdisen rating scale [1] may be additionally employed. Four- to six-monthly serum lithium levels should also be carried out. Routine blood tests, such as lipid levels to ascertain the cardiac status, and taking any risk factors into consideration, should be done early to prevent the above stated cardiac effects. In addition, lithium should be properly considered when administered to patients with pre-existing hyperlipidaemia, hypertension, smoking, diabetes and family history of ischaemic heart disease. This is because lithium clearance may be disrupted by conditions which affect renal function, namely diabetic nephropathy and hypertension, which will in turn predispose them to lithium toxicity [2]. Medications that could minimise lithium removal, which include non-steroidal anti-inflammatory drugs (NSAIDs), thiazide diuretics, ACE inhibitors and ARBs, should not be taken with lithium.

In a patient presenting with ECG changes, a primary survey of their airway and breathing should be done, followed by the termination of lithium administration. Lithium should be replaced with another mood stabiliser like valproate or lamotrigine. It is important to take precautions if the need to restart lithium arises as these ECG changes may recur [11]. Fatal cardiac outcomes usually stem from lithium toxicity but as a general rule, the cases involving non-fatal outcomes do not require changes in their lithium dosage [2]. Certain changes in the ECG, including atrioventricular and bundle branch blocks, as well as QTdR increase, have not been shown to precede any significant outcome, even after years of persistence [2]. However, the risk for subsequent arrhythmias is greater in those reported with sinoatrial blocks, changes in ST segment and Brugada pattern [2]. It is in these patients that the dosage of lithium must be titrated down or even discontinued and replaced with another mood stabiliser [2], as was duly done in both our patients. Hypothyroidism should also be looked out for during the course of treatment with lithium [1]. This can be done by looking out for any signs and symptoms of hypothyroidism such as fatigue, weakness, cold intolerance, in addition to a thyroid function test for confirmation.

Conclusions

The benefits of lithium outweigh the cardiac risks it poses on an individual's health. Early detection would be to have a baseline ECG and thence, cardiac monitoring on a regular basis [2]. The cardiac effects are generally

rare, reversible and do not affect heart performance.

Lithium use is not contraindicated in those having heart problems but its monitoring should be compulsory to ensure safety [13]. However, lithium should be discontinued if persistent cardiac side-effects occur.

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